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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,173	03/16/2001	Bernard Charles Sherman	PT-1896000	3792

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	**PAPER NUMBER**
1615	13

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/809,173	Applicant(s) SHERMAN, BERNARD CHARLES	
	Examiner Humera N. Sheikh	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003 (paper no. 12)* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Receipt of the request for extension of time (3 months) and the Amendment, both filed 06/12/03 is acknowledged.

Claims 1-18 are pending. Claims 1 and 14 have been amended. No claims have been added or cancelled. Claims 1-18 remain rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu *et al.* (Pharm. Research, Vol. 7, No. 4, pgs. 379-383) *in view of* Harris *et al.* (US Pat. No. 4, 743,450).

Gu teaches a process wherein moexipril hydrochloride is stabilized by reacting the moexepril hydrochloride with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate (see reference pages 379-383 and Tables). Gu teaches that through the wet granulation procedure, alkalizing agents were found to be effective in stabilizing moexipril hydrochloride in the solid state (pg. 383, col. 1). It is postulated that the stabilization results from the neutralization of the acidic drug by basic excipients at the outer surface of the granulated material. In addition, Gu teaches that it is also possible that a portion of the moexipril hydrochloride was converted to the cation salts through granulation and these cation salts degraded much slower in the solid state (pg. 383, cols 1-2).

Gu while teaching the reaction between moexipril hydrochloride and an alkaline stabilizing agent does not teach the use of an alkaline magnesium compound in the process.

Harris teaches a process of making a solid pharmaceutical composition comprising a method of stabilizing ACE inhibitor drugs (enalapril, quinapril, indolapril) in combination with an alkaline magnesium compound - magnesium carbonate as the

stabilizer, acid addition salts (hydrochloride), a solvent (water) and various excipients (see reference column 1, lines 15-63); (col. 3, line 60 through col. 4, line 68). The instability of the ACE inhibitor drugs can be stabilized by including an alkaline stabilizer. Salts of alkali and alkaline earth metals are operable, however magnesium, calcium and sodium are preferred, wherein magnesium is most preferred (col. 3, lines 25-39). The amount of stabilizer used will be between 1% and 90% (col. 3, lines 40-45). Examples A, B and D demonstrate tablets comprising an ACE inhibitor (quinapril) in combination with a stabilizer (magnesium carbonate) wherein a wet granulation method was used. Since a wet granulation procedure was used, one of ordinary skill in the art would have expected the ACE inhibitor drug and the alkaline compound to react through ionic interactions.

Therefore it would have been obvious to one of ordinary skill in the pharmaceutical art at the time the invention was made to include an alkaline stabilizer, particularly an alkaline magnesium compound as instantly claimed, with an ACE inhibitor drug because the active ingredients or drugs will be preserved from cyclization and hydrolysis and in addition will have greater storage stability and be rendered more suitable for use in drug combinations. The expected result would be an improved stabilized composition for the effective treatment of hypertension.

Regarding the percentage of conversion of the ACE inhibitor, no criticality is seen in the specified amounts, since the examples taught by Harris et al. demonstrate that the amount of magnesium carbonate is much greater than the amount of quanipril

hydrochloride in the formulation. For instance, Example A shows a quanipril hydrochloride content of 5.4 mg compared to the 46.6 mg of magnesium carbonate (see col. 4). Similarly, Example B shows a quanipril hydrochloride content of 43.4 mg relative to the magnesium carbonate content of 250.0 mg. Example D also contains greater amounts of magnesium carbonate than quanipril hydrochloride (col. 5). Furthermore, Harris teaches that the amount of stabilizer used will be between 1% and 90% (col. 3, lines 40-45).

Response to Arguments

Applicant's arguments filed 06/12/03 have been fully considered but they are not persuasive. The applicant argued, "No reaction process is taught, components are merely combined and any reaction is insignificant to the desired end result. Gu does not motivate one skilled in the art to manufacture moexipril magnesium through Gu's teaching of manufacturing moexipril hydrochloride stabilized with an alkaline stabilizing agent. Nowhere in the 4,743,450 is there discussed any reactions or reference of moexipril magnesium. A solvent must be present in an amount as to convert at least 70% of the moexipril acid addition salt to moexipril magnesium. There is no motivation or reason suggested by the prior art to make any changes. Applicant is not "combining" but "reacting" the active and the agents to result in moexipril magnesium."

The applicants' arguments have been fully considered, but were not found to be persuasive. Gu teaches a process wherein moexipril hydrochloride is stabilized by reacting the moexepril hydrochloride with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate. Gu does not teach the use of an alkaline magnesium compound in the process. The secondary reference of Harris was relied upon for the teaching of an alkaline magnesium compound. Harris explicitly teaches a process of making a solid pharmaceutical composition, which comprises a method of stabilizing ACE inhibitor drugs (enalapril, quinapril, indolapril) in combination with an alkaline magnesium compound - magnesium carbonate as the stabilizer, acid addition salts (hydrochloride), a solvent (water) and various excipients. The instability of the ACE inhibitor drugs can be stabilized by including an alkaline stabilizer. Salts of alkali and alkaline earth metals are operable, however magnesium, calcium and sodium are preferred, wherein magnesium is most preferred. It is the position of the examiner that the claims do not recite any material which is distinct from the art. The applicant's argument that a *combination* or ingredients rather than a *reaction* is taught is not persuasive. The term "reacting" is generic. One definition of "reacting" is the *interchange of constituents with other substances*. The mixing of the ingredients (as taught by Gu and Harris) constitutes this interchange. The applicant has the burden of showing distinguishing aspects of the claimed invention versus the prior art.

The applicant's argument that the conversion of at least 70% of the moexipril acid addition salt to moexipril magnesium is not taught was not persuasive since, one of ordinary skill in the art would be capable of determining suitable percents of conversion

based on the intended purpose utilizing routine or manipulative experimentation. Furthermore, generally differences in concentration (or temperature) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Gu teaches a process wherein moexipril hydrochloride is stabilized by reacting the moexepril hydrochloride with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate. Gu is deficient in the sense that he does not teach an alkaline magnesium compound in the process. The secondary reference of Harris was relied upon for the teaching of an alkaline magnesium compound.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon

hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The prior art teaches a similar process as instantly claimed. Hence, the instant invention is deemed obvious and unpatentable over the combined references of Gu and Harris.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns

August 19, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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